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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,793	02/16/2001	Bertrand Seraphin	70436	5538

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EXAMINER

HINES, JANA A

ART UNIT PAPER NUMBER

1645

DATE MAILED: 04/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,793	SERAPHIN ET AL.	
	Examiner	Art Unit	
	Ja-Na Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-11 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 24, 2004 has been entered.

Amendment Entry

2. The amendment March 24, 2004 has been entered. Claims 1-11 have been amended. Claims 1-11 are under consideration in this office action.

Withdrawal of Rejections

3. The following rejections have been withdrawn in view of applicants' amendments and arguments:

- a) The rejection of claims 1-9 and 11 under 35 U.S.C. 102(b) as being anticipated by Darzins et al., (WO 96/40943); and
- b) The rejection of claim 10 under 35 U.S.C. 103(a) as being unpatentable over Darzins et al., (WO 96/40943) in view of Zheng et al.

Response to Arguments

4. Applicant's arguments with respect to claims 1-11 have been considered but are moot in view of the new ground(s) of rejection.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting and/or purifying biomolecules and/or protein complexes from a yeast host, the method comprising: (a) providing a vector encoding a fusion of a yeast protein to the Calmodulin Binding Peptide-Tobacco Etch Virus protease NIA –Staphylococcus Protein A (CBP-TEV-Protein A) double tag wherein the fusion protein is one subunit of a protein complex of yeast containing 24 subunits and the plasmid is transformed in to the yeast cell; (b) maintaining the expression environment under conditions that facilitate expression of the proteins in a native form which retains their biological activity as fusion proteins with affinity tags, and under conditions that allow the formation of a complex between the subunits; (c) purifying the one or more subunits by combinations of at least two

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different affinity purification steps each comprising binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the one or more subunits from the support material after substances not bound to the support material have been removed wherein the first affinity step allows purification by binding to IgG linked beads, eluting the TEV protease cleavage binding of the eluted material on calmodulin containing beads and the second affinity step comprises calmodulin affinity elution; (d) concentrating the eluted proteins using precipitation techniques; and (e) detecting the concentrated proteins by polyacrylamide gel electrophoreses, does not reasonably provide enablement for a method for detecting and/or purifying biomolecules and/or protein complexes the method comprising: (a) providing an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex, the subunits being fused to at least two different affinity tags, one of which consists of one or more IgG binding domains of Staphylococcus protein A; (b) maintaining the expression environment under conditions that facilitate expression of the one or more subunits in a native form as fusion proteins with affinity tags, and under conditions that allow the formation of a complex between the one or more subunit and other components capable of complexing with the one or more subunits; (c) detecting and/or purifying the one or more subunits by combinations of at least two different affinity purification steps each comprising binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the one or more subunits from the support material after substances not

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bound to the support material have been removed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with these claims.

The specification, beginning at page 16 teaches that certain conditions are required to achieve the claimed method of detection and purification. The examples recite that a method comprises providing a vector encoding a fusion of a yeast protein to the Calmodulin Binding Peptide-Tobacco Etch Virus protease NIA –Staphylococcus Protein A (CBP-TEV-Protein A) double tag wherein the fusion protein is one subunit of a protein complex of yeast containing 24 subunits and the plasmid is transformed in to the yeast cell. The example also teaches that the expression environment should be maintained under conditions that facilitate expression of the proteins in a native form which retains their biological activity as fusion proteins with affinity tags, and under conditions that allow the formation of a complex between the subunits. The examples teach that purification of one or more subunits by combinations of at least two different affinity purification steps comprises binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the one or more subunits from the support material after substances not bound to the support material have been removed wherein the first affinity step allows purification by binding to IgG linked beads, eluting the TEV protease cleavage binding of the eluted material on calmodulin containing beads; while the second affinity step comprises calmodulin affinity elution; concentrating the eluted proteins using precipitation techniques; and detecting the concentrated proteins by polyacrylamide gel

electrophoreses. Thus undue experimentation would be required to determine all the steps and variables which could affect the claimed method of detection and purification.

The teaching within the specification is limited to the specific steps and reagents recited in the instant specification. The specification fails to teach examples of detection and purify biomolecules and protein complexes, such that without the exact and precise method steps and specific reagents the claimed detection and purification methods could not be achieved. The broad method claims do not require the precise and active steps and reagents thus, one of ordinary skill in the art would be required to determine the appropriate reagents and conditions required to achieve the claimed method.

Therefore, the specification fails to enable a method for detecting and/or purifying biomolecules and/or protein complexes the method comprising: (a) providing an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex, the subunits being fused to at least two different affinity tags, one of which consists of one or more IgG binding domains of Staphylococcus protein A; (b) maintaining the expression environment under conditions that facilitate expression of the one or more subunits in a native form as fusion proteins with affinity tags, and under conditions that allow the formation of a complex between the one or more subunit and other components capable of complexing with the one or more subunits; (c) detecting and/or purifying the one or more subunits by a combinations of at least two different affinity purification steps each comprising binding the one or more subunits via one affinity tag to a support material capable of selectively binding one of the affinity tags and separating the one or more subunits from the

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support material after substances not bound to the support material have been removed.

The claim language drawn to heterologous nucleic acids encoding one or more subunits of a biomolecule complex appears to embrace sequences without disclosing the actual nucleic acid sequences. Without such information, one of skill in the art could not predict which heterologous nucleic acids^{which} would result in the desired encoded one or more subunits of a biomolecule complex, thereby requiring undue experimentation.

Without such information, one of skill in the art could not predict which method steps would result in the desired subunits. Accordingly, one of skill in the art would be required to perform undue experimentation to use the claimed method for detecting and/or purifying biomolecules and/or protein complexes the method under the recited conditions. Therefore, one skilled in the art could not make and/or use the invention without undue experimentation.

6. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are drawn to a method for detecting and/or purifying biomolecule and/or protein complexes the method comprising in pertinent part providing an

expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecules complex.

The specification and claims still lack sufficient written description of the generically claimed expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule complex. The one or more heterologous nucleic acids are defined by its activity of function, i.e., the ability to encode one or more subunits of a biomolecule complex. While the description of the ability of the claimed heterologous nucleic acids which encode may generically describe the heterologous nucleic acid's function, it does not describe the nucleic acid itself. The encoding distinction is a purely functional distinction. Thus, a description of the heterologous nucleic acid by what it does, such as encoding one or more subunits of a biomolecule complex is insufficient. It is noted that the specification fails to disclose an example of heterologous nucleic acid sequences which can be used in the claimed method.

The specification does not provide evidence that any heterologous nucleic acid, as claimed, functions with the ability to encode one or more subunits of a biomolecule complex. The instant specification and claims are encompassing currently unknown sequences and claiming that these nucleic acid sequences can be used in the method of detection and purification. Therefore is evidence that other heterologous nucleic acids have not yet been identified. Moreover, the instant specification fails to disclose specific heterologous nucleic acid sequences; rather the specification broadly defines the sequences to be any and every nucleic acid sequence without any

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discretion. In view of the lack of evidence, it is apparent that Applicants were not in possession of all or many heterologous nucleic acid sequences additional primers that encode one or more subunits of a biomolecule complex at the time of filing the instant application. The skilled artisan cannot envision the detailed structure of a method for detecting and/or purifying biomolecule and/or protein complexes the method comprising in pertinent part providing an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecules complex, thus conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

An adequate description requires more than a mere statement that it is part of the invention. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Encoding distinguishes the claimed nucleotide sequences from unclaimed sequences only by what they do, which is a purely functional distinction. Even where there is an actual reduction to practice, which may demonstrate possession of an embodiment of an invention, it does not necessarily describe what the claimed invention is. The instant claims describe a heterologous nucleic acid sequence is described by its function i.e., encoding, however this description does not describe the claimed heterologous nucleic acids themselves. See also, *In The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), where the court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants

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are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Thus, in the absence of a method for detecting and/or purifying biomolecule and/or protein complexes the method comprising in pertinent part providing an expression environment containing one or more heterologous nucleic acids encoding one or more subunits of a biomolecule: complex adequately described, an heterologous nucleic acid described only by its ability to encode fails to meet the written description requirements. Therefore the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

7. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 is unclear. Step (a) recites that the subunits are fused to at least two different affinity tags, one of which consists of one or more IgG binding domains of Staphylococcus protein A; while step recites (b) facilitating expression of the one or more subunits in a native form as fusion proteins with affinity tags. It appears that step

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(a) recites that the subunits are being fused to the affinity tags while step (b) appears to be reciting that the expression creates fusion proteins. Therefore it is unclear whether there is a step that fuses the subunits to the affinity tags followed by another expression to achieve the fusion proteins, or if applicants are claiming a different sequence of events. Therefore clarification is required to overcome the objection.

9. The term "other components" in claim is a relative term which renders the claim indefinite. The term "other components" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. There is no recitation of exactly these other components are. The metes and bounds of the term is unclear since there is no requisite definition of what the other components consist of or what components are included or excluded from the term other components.

Therefore clarification is required to overcome the rejection.

10. The preamble of the claims is drawn to a method for detecting and/or purifying biomolecules and/or protein complexes, however the recited steps fail to teach how the biomolecules and/or proteins can be detected. There is no detection step which correlates the method for detecting and/or purifying biomolecules and/or protein complexes to actual detection. Therefore, the goal of the preamble is not commensurate with the steps of the method that are drawn to detecting biomolecules and/or protein complexes.

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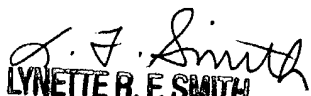
11. Claims 1-11 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The detection step is omitted. The claim ends with purification steps and fails to recite a detection step. A positive recitation of all the necessary method steps is required. Therefore the claim is rejected for failing to recite how the detection of the biomolecules and or protein complexes can occur.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ja-Na Hines
April 21, 2004


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